SYNTHESIS AND SPECTRAL STUDIES OF SOME BIOACTIVE HETEROCYCLES WITH SULFONYL GROUP

A PROPOSED RESEARCH PLAN IN PARTIAL FULFILLMENT
FOR THE AWARD OF THE DEGREE
OF
DOCTOR OF PHILOSOPHY
IN
SCIENCE
MODY UNIVERSITY OF SCIENCE AND TECHNOLOGY

Supervisor:

Dr.S.S.Chauhan

(Department of Chemistry)

Submitted by:

Ms. Sandhya Chhakra

Enroll. No.-150735

College of Arts, Science & Humanities

Lakshmangarh, Sikar – 332311 (Rajasthan)

CONTENTS

1.		INTRODUCTION	1-2
2.		SCOPE OF THE WORK	2-3
3.		OBJECTIVES OF THE PRESENT WORK	3-4
	3.1	General Objectives	4
	3.2	Specific Objectives	4-5
4.		LITERATURE REVIEW	5
	4.1	β-Diketones /β-Ketoesters	5-6
	4.2	Application of β-Diketones /β-Ketoesters and their Heterocycles Table 1: Some Marketed Drugs of Heterocycles	7-8
5.		WORK PLAN & METHODOLOGY (Year wise plan of research work)	8-9
6.		WORK ALREADY DONE	10-11
7.		REFERENCES	12-15

1. INTRODUCTION

The chemistry of heterocycles has attracted much interest because of their role in the biologically active moieties. Our interest in the synthesis of heterocyclic compounds encouraged us to undertake the synthesis of several sulphur, nitrogen and oxygen heterocycles. Among a wide variety of sulphur, nitrogen and oxygen heterocycles that have been explored for developing pharmaceutically important molecules.

Organic heterocyclic compounds are those in which at least one of the ring atom is carbon, the other being considered the hetero atom; carbon is still by far the most common ring atom in heterocyclic compounds. Hetero atom have significantly different electronic properties than carbon atoms. They have higher electronegativity, possess lone pair of electrons, and are capable of forming bonds with hydrogen. Because of these properties, they often play crucial role in the binding of drugs with the receptors and thus affect significantly the activity of drugs. The presences of one or more hetero atoms with the carbocyclic analogues are responsible for better biological activities in the heterocycles as compared to their carbocyclic analogues.

The importance of β-diketones/ β-ketoesters in synthetic organic chemistry is difficult to overstate. β-Diketones/ β-ketoesters are stable, usually nontoxic and therefore convenient for storage and use. They serve as precursors for the synthesis of large number of biologically active heterocyclic compounds such as diazepines, benzodiazepines, benzothiazepine, pyrazoles, isoxazoles, imidazole and benzimidazole[1-4]. At the same time, they possess a broad spectrum of useful and sometimes unique chemical properties, which makes them extremely attractive as an intermediates for synthetic organic chemistry. Aside from their synthetic importance, they play a vital role as building blocks for construction of broad diversity of natural products including aromatic and many heterocycles[5-7].

Compounds containing sulfonyl group have also been a research focus as a result of their biological importance and chemical applications. Sulfones occupy a unique position in the drug industry with their many biological activities[8-9].

2. SCOPE OF THE WORK

More than half of the natural compounds are heterocyclic in nature. In the biological world, heterocyclic compounds are present everywhere e.g. various coenzymes, proteins and carbohydrates. Many heterocyclic compounds are biosynthesized by plants and animals and are biologically active. Over million of years these organisms have been under intense evolutionary pressure and their metabolites may be used for advantage. Some heterocycles are fundamental to life,

such as *heam* derivatives in blood and *chlorophyll in plants, which is* essential for photosynthesis. Similarly, the paired bases found in RNA and DNA are heterocycles.

The majority of pharmaceuticals, pesticides and dye stuffs contain heterocyclic rings. They are widely distributed in nature and are essential to life. Dyestuffs of plant origin include indigo blue used to dye jeans. A novel poison detected fame is *strychnine* obtained from the plant *Strchnos nux-vomica.* Some other natural products e.g. *morphine, nicotine, pyridoxine and cocaine* also contain heterocyclic ring. There are thousands of other natural and synthetic heterocyclic compounds of major importance, are being used as medicine and in most of the other valuable activities known to man.

A brief survey of the literature indicated that the synthesis of new heterocyclic compounds like diazepines, benzodiazepines, benzothiazepines, pyrazoles and isoxazoles has acquired greater importance. Keeping in view of versatile and important medicinal utility of these compounds it was considered worthwhile to synthesize novel heterocycles through β-diketones [1-6] as the precursors for their synthesis.

3. OBJECTIVES OF THE PRESENT WORK

The coverage of heterocyclic chemistry is vast and constitute important domain for the society viz. energy, environment, biology, medicine, agribusiness and

materials. Heterocyclic chemistry with its multidimensional role interacts with other numerous disciplines e.g. cosmetics, reprography, information storage and plastics. The trend towards the synthesis, design, characterization and application of heterocyclic compounds is undoubtedly increasing.

3.1. General Objectives

1. Develop experience to handle and use chemicals.
2. Develop the skill of independent laboratory work.
3. Develop the skill of synthesis.
4. Develop the skill of separation and purification of compounds.
5. Develop the skill of analysis techniques.
6. Acquire knowledge of how to deal with the research or project work.

3.2. Specific Objectives

1. Designing of novel β-diketones.
2. Designing of novel Heterocycles.
3. Synthesis and purification of β-diketones intermediate and their heterocyclic compounds.

4. Characterization of these compounds by Elemental analysis and melting point determination.

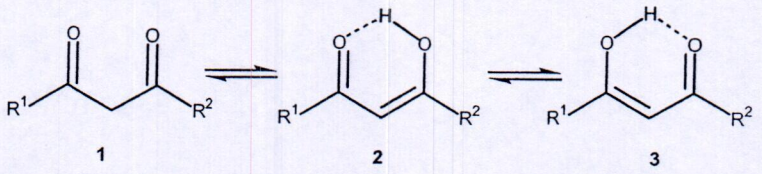
5. Interpretation of spectroscopic spectra, like IR, NMR and MS.

6. Elucidation of structural formula and theoretical explanations from the literature surveys.

4. LITERATURE REVIEW

4.1 β-Diketones /β-Ketoesters

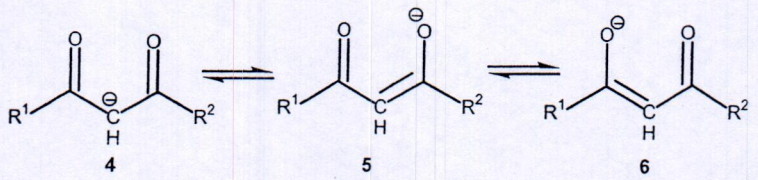
The chemical reactivity of β-diketones is based on the duality of their molecular structure. Keto-enol tautomerism is one of the salient features of β-diketones. Normally, enolisable 1,3-diketones exist in solution or in solid phase state as keto-enol tautomers (1, 2, and 3).

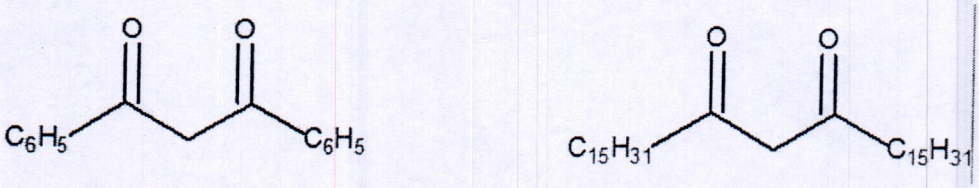


1 2 3

The equilibrium point between keto-enol tautomers depends strongly on the nature of substituents, conformational effects, polarity of media, and temperature. In the presence of a strong base like sodium ethoxide, sodium methoxide, sodamide etc.,

both the keto and enol form of the β-diketone lose a proton to form enolateion (4, 5 and 6).





[7] [8]

Many naturally occuring 1,3-diketones, even such simple ones as dibenzoylmethane (DBM)(7) and n-tritriacontane-16,18-dione (TTAD) (8) possess a broad spectra of biological activity. These beta-diketones and their closest structural derivatives appear in many plants, for example, in *Eucalyptus leafs*[10] and *Licoricl*[11]. Other long chain aliphatic β-diketones are found in *Vanilla* beans[12] and *Sunflower* pollen[13]. All mentioned β-diketones are powerful natural antioxidants and possess prominent anticancer properties with minimal toxicity[14-18].

4.2 Application of β-Diketones /β-Ketoesters and their Heterocycles

A brief survey of the literature indicated that the synthesis of new heterocyclic compounds like diazepines, benzodiazepines, benzothiazepines, pyrazoles and isoxazoles has acquired greater importance. Keeping in view of versatile and important medicinal utility of these compounds it was considered worthwhile to synthesize novel heterocycles through β-diketones and β-ketoester[1-18] as the precursors for their synthesis. Attempts were made to synthesize various pharmacophoric diversities, of some heterocyclic derivatives e.g. diazepines, benzodiazepines, benzothiazepines, pyrazoles, isoxazole and many other important molecule in our laboratory[19-22].

Table -1: Some Marketed Drugs of Heterocycles.

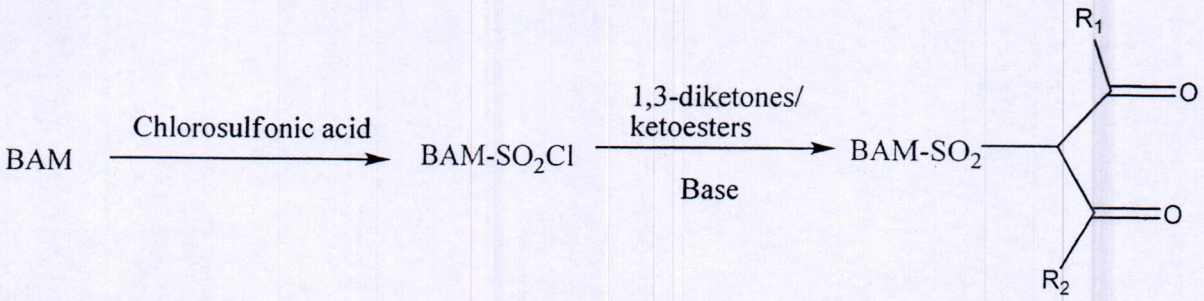
S.No.	Chemical Name	Trade Name	Biological Activities
1.	Alprazolam	Xanax	Anxiolytic[23]
2.	Chlordiazepoxide	Librium	Anxiolytic[24], Tranquilizer[25]
3.	Clonazepam	Klonopin	Anticonvulsant[26]
4	Temazepam	Restoril	Sedative and hypnotic[27]
5	Triazolam	Halcion	Sedative and Hypnotic[28]
6	Sulfisoxazole	Sulfoxol, Sosol, Sulfafurazole	Antibacterial[29]

7	Drazoxolon	PP 781, Ganocide, Mil-Col, Saisan	Fungicide[30]
8	Zonisamide	AD-810, CI-912, Aleviatin, Excegram, Exceglan	Anticonvulsant and neurotoxic[31]
9	Acetyl Sulfisoxazole	Gantrisin Acetyl	Antibacterial[32]
10	Cycloserine	Micoserina, Oxamycin, Seromycin, Orientomycin	Antibacterial[33]

5. WORK PLAN & METHODOLOGY

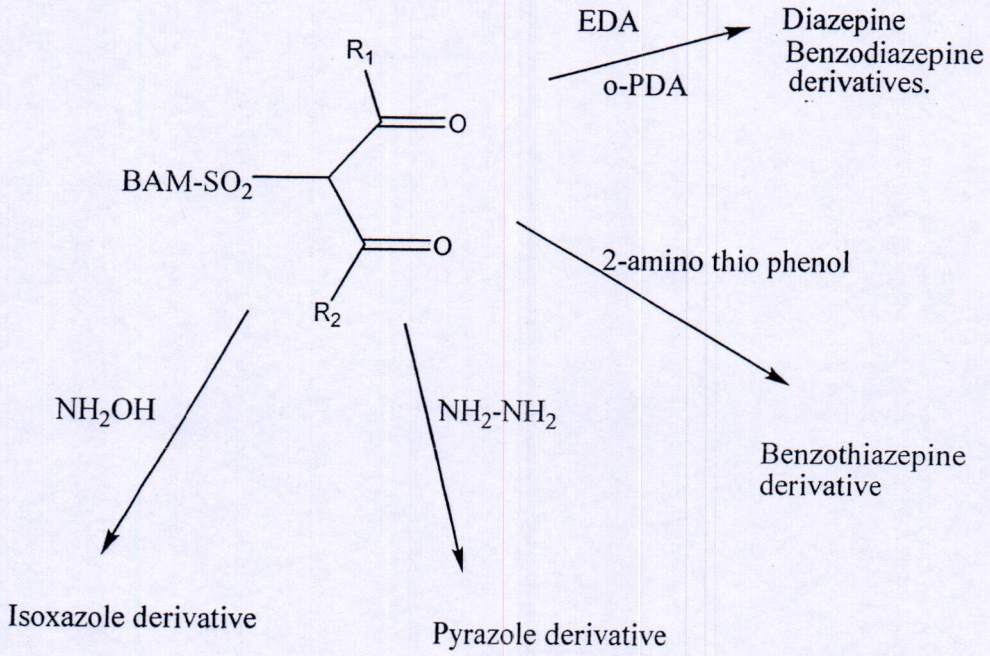
In view of the medicinal importance of heterocyclic compounds, we would propose to synthesize various new heterocyclic compounds by reacting various new β -diketones or β-ketoesters with 2-amino benzenethiol, hydrazine and hydroxylamine.

(a) Synthesis of various β-diketones and β-ketoesters.



BAM=biologically active moieties
R_1 = CH_3, C_6H_5, OC_2H_5
R_2 = C_6H_5, OC_2H5, CH_3

(b) Reaction of different β-diketones and β-keto esters with various diamine/substituted diamine, 2-amino thio phenol.



(c) Attempts would also be made to synthesize substituted other different types of novel biologically important heterocycles, if possible and time permits.

Year wise plan of research work

Autumn Semester 2015-16	Review of Literature & Course Work
Spring Semester 2015-16	Review of Literature, Course Work and synthesis of 5 new β-diketones and β-ketoesters.
Autumn Semester 2016-17	Review of Literature, Course Work and Synthesis of 3 heterocyclic compounds
Spring Semester 2016-17	Comprehensive Examination / Research Plan Synthesis and characterization of new heterocyclic compounds series I
Autumn Semester 2017-18	Synthesis and characterization of new heterocyclic compounds series II & writing of introduction part.
Spring Semester 2017-18	Synthesis and characterization & Writing of thesis.

6. WORK ALREADY DONE

(a) Synthesis of 5 new β-diketones and β-ketoesters

7. REFERENCES

1. A. Puratchikody, V. Sivajothi, A. Jaswanth, K. Ruckmani, M. Nallu; *Indian Journal of Heterocyclic Chemistry* **2002**, 11 (3) 241-242, Prof. R.S. Verma; C.A. 137, , 63204n, **2002**.

2. J. Thiele, G. Stimming; *Ber.*, 40, 955, **1907**.

3. H. Plieninger, J. Nogradi; *Ber.*, 88, 1965, **1956**.

4. D. Lloyd, D.R. Marshall; *J. Chem. Soc.*, 2597, **1956**.

5. T.N. Ghosh; *Journal Indian Chemical Soc.*, 10, 583, **1933**.

6. T.M. Harris, C.M. Harris; *Tetrahedron.*, 33, 2159, **1977**.

7. G.P. Ellis, *Chromanones*; *Chromanones and Chromones*; *Wiley* : *New York.*, **1977**.

8. J. Mann: *Secondary Metabolism* : *Second Ed*; *Oxford University Press* : *New York.*, **1987**.

9. D.Q. Shi, J.A. Liu, X.P. Liu, J.H. Wang; Ying Yong Huaxul, 20, 130, 2003; *Chem. Abstr.*, 138, 368830z, **2003**.

10. E. Titus, Bernstein; *J. Ann. N.Y. Acad. Sci.*, 52, 719, **1949**.

11. T. Osawa, Y. Sugiyama, M. Inayjoshi, S. Kawakishi; *ACS Symposium Series.*, 183, 547, **1994**.

12. C.C. Lin, Y.P. Lu, Y.R. Lou, C.T. Ho, H.H. Newmark, C. MacDonald, K.W. Singhletary, M.T. Huang; *Cancer Lett.*, 125, 168, **2001**.

13. B.R. Ramarson, E.M. Gaydou, I. Bombarda; *J. Agric. Food. Chem.*, 48, 4739, **2000**.

14. S. Schulz, C. Arsene, M. Tauber, J.N. McNeil; *Phytochemistry.*, 54, 325, **2000**.

15. M. Hirose, K. Ozaki, K. Takaba, S. Fukushima, T. Shirai N. Ito.; *Carcinogenesis.*, 12, 1917, **1991**.

16. K. Takaba, M. Hirose, Y. Yoshida, J. Kimura., Ito, N., *Cancer Lett.*, 39, 113, **1997**.

17. A. Puratchikody, V. Sivajothi, A. Jaswanth, K. Ruckmani, M. Nallu; *Indian Journal of Heterocyclic Chemistry,* 11(3), 241-242, **2002**.

18. B. Talapatra, S.K. Mandal, K. Biswas, R. Chakrabarti, S.K. Talapatra; *Journal of Indian Chemical Society,* 78, 765, **2001**.

19. R. Unny, P. Joshi, M.P. Dobhal, Y.C. Joshi; *Heterocyclic Communications,* 9,2, **2003**.

20. Y. C.Joshi, P. Joshi, S.S. Chauhan, S. Nigam; *Heterocyclic Communications,* 10,249, **2004**.

21. S. S. Chauhan, Y. C. Joshi; *An Indian Journal of Organic Chemistry*,4, 5, **2009**.

22. S. S. Chauhan, Y. C. Joshi; *RasayanJChem.*,1, 475, **2008**.

23. A. Walser, G. Zenchoff; *J. Med. Chem.*, 20, 1694, **1977**.

24. Sternbach, Reeder; *J. Org. Chem.*, 26, 1111, **1961**.

25. K. Florey; *Academic Press, New York*, 15-51, **1972**.

26. S. Ebel, H. Schutz; *Ibid*, 27, 325, **1977**.

27. R.C. Heel *et al.* : "Review of Pharmacology"; *Drugs*, 21, 321-340, **1981**.

28. G.E. Pakes *l.*, "*Review of pharmacology and therapeutic efficancy'*; *Drugs,* 22, 81-110, **1981**.

29. B.C. Rudy, B.Z. Senkowski; *Academic Press, New York*, PP-487-506, **1973**.

30. Anderson, Horsgood; *Soil Biol. Biochem.*, 3, 271, **1971**.

31. Y. Masuda ; *Epilepsia*, 20, 623, **1979**.

32. Hoffer : (1955 to Hoffmann – La Roche); U.S. Pat. 2,721, 200, **1955**; *Merck Index*; 16, 100, **1989**.

33. Kuehl, Jr; *J.Am.Chem.Soc.*,77, 2344, **1955**.